PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#19

Re: U.S. Patent 5,298,520
Issued: March 29, 1994
To: Raymond Baker, Victor G. Matassa, and Leslie J. Street
Assignee: Merck Sharp & Dohme Limited
For: Triazole Containing Indole Derivatives

Assistant Commissioner of Patents
Washington, DC 20231
Attn: Box Patent Extension

Re: Deposit Account 13-2755
MERCK & CO., Inc.
U.S. Patent 5,298,520

Sir:

Transmitted herewith is the application for extension of patent term under 35 U.S.C. 156 with regard to U.S. Patent 5,298,520.

Please charge our Deposit Account No. 13-2755 in the amount of $1,090.00. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Account No. 13-2755. Duplicate copies of this sheet are enclosed.

Respectfully submitted,

Philippe L. Durette

Philippe L. Durette
Reg. No. 35,125
Attorney for Applicants

MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-4568

Date: August 5, 1998

IN TRIPLICATE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re: U.S. Patent 5,298,520
Issued: March 29, 1994
To: Raymond Baker, Victor G. Matassa, and Leslie J. Street
Assignee: Merck Sharp & Dohme Limited
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Assistant Commissioner of Patents
Washington, DC 20231
Attn: Box Patent Extension

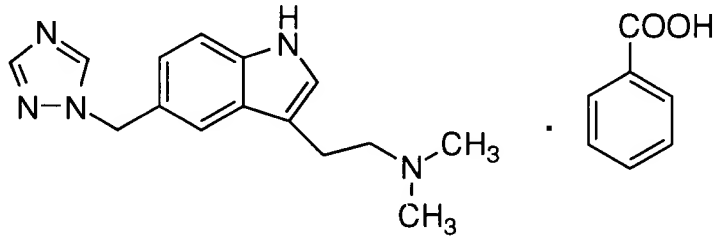
APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Sir:

Your Applicant, Merck & Co., Inc., a corporation organized and existing under the laws of the state of New Jersey, represents that, by Authorization of Agent/Power of Attorney enclosed herein (Attachment A), it is submitting the instant application as agent acting on behalf of Merck Sharp & Dohme Limited, assignee of the entire interest in and to Letters Patent of the United States Patent 5,298,520, granted to Raymond Baker, Victor G. Matassa, and Leslie J. Street on March 29, 1994 for "Triazole Containing Indole Derivatives" by virtue of an assignment in favor of Merck Sharp & Dohme Limited, recorded November 24, 1993, Reel No. 6781, Frame No. 0298. Your Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. 156 by providing the following information required by the rules promulgated by the United States Patent and Trademark Office (37 C.F.R. 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format which will follow the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

(1) The approved products MAXALT® (Rizatriptan Benzoate) and MAXALT-MLT™ (RAPIDISC) (Rizatriptan Benzoate) contain

as the active ingredient rizatriptan benzoate having the chemical name *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate (alternative name is *N,N*-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine benzoate). The structural formula for rizatriptan benzoate is as shown below:



(2) The approved products were subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. 355).

(3) The approved products, MAXALT® (Rizatriptan Benzoate) and MAXALT-MLT™ (RAPIDISC) (Rizatriptan Benzoate), received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on June 29, 1998.

(4) The only active ingredient in MAXALT® (Rizatriptan Benzoate) and MAXALT-MLT™ (RAPIDISC) (Rizatriptan Benzoate) is rizatriptan benzoate, which has not been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 20-864 and NDA 20-865 by the Food and Drug Administration on June 29, 1998.

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. 1.720(f), said period will expire on August 28, 1998.

(6) The complete identification of the patent for which extension is being sought is as follows:

Inventors: Raymond Baker, Victor G. Matassa, and Leslie J. Street

Patent Number: U.S. Patent 5,298,520

Issue Date: March 29, 1994

Expiration Date: January 28, 2012

(7) See "Attachment B" for a complete copy of the patent identified in paragraph (6) hereof and Certificate of Correction.

(8) See "Attachment C" for a copy of a receipt for maintenance fee payment.

(9) U.S. Patent 5,298,520 claims the approved products. Specifically, the active ingredient, rizatriptan benzoate, is claimed in Claims 1 and 2; the method of treatment utilizing the active ingredient, rizatriptan benzoate, is claimed in Claims 5 and 6; and the pharmaceutical composition containing the active ingredient, rizatriptan benzoate, is claimed in Claims 3 and 4.

Claim 1 reads as follows:

1. The compound which is *N,N*-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine or a pharmaceutically acceptable salt thereof.

The approved products contain rizatriptan benzoate which is a pharmaceutically acceptable salt of the compound of Claim 1.

Claim 2 reads as follows:

2. A salt of the compound according to claim 1 selected from the group consisting of the oxalate, benzoate, and hydrochloride salts.

The approved products contain rizatriptan benzoate which is the pharmaceutically acceptable benzoate salt of the compound of Claim 1.

Claim 3 reads as follows:

3. A pharmaceutical composition, comprising a therapeutically effective amount of *N,N*-dimethyl-2-[5-(1,2,4- triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier or excipient.

The approved products are pharmaceutical compositions containing as active ingredient rizatriptan benzoate which is a pharmaceutically acceptable salt of *N,N*-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine.

Claim 4 reads as follows:

4. A pharmaceutical composition according to claim 3 wherein the pharmaceutically acceptable salt is selected from the group consisting of the oxalate, succinate, benzoate, and hydrochloride salts.

The approved products are pharmaceutical compositions containing as active ingredient rizatriptan benzoate which is the pharmaceutically acceptable benzoate salt of *N,N*-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine.

Claim 5 reads as follows:

5. A method for the treatment of migraine, cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and pediatric migraine, which comprises administering to a patient in need of such treatment an effective amount of *N,N*-dimethyl-2-[5-(1,2,4- triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine or a pharmaceutically acceptable salt thereof.

The approved products contain as active ingredient, rizatriptan benzoate, which is indicated for the acute treatment of migraine attacks, and which is a pharmaceutically acceptable salt of *N,N*-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine.

Claim 6 reads as follows:

6. A method according to claim 5 wherein the pharmaceutically acceptable salt is selected from the group consisting of the oxalate, succinate, benzoate, and hydrochloride salts.

The approved products contain as active ingredient, rizatriptan benzoate, which is indicated for the acute treatment of migraine attacks, and which is the pharmaceutically acceptable benzoate salt of *N*,*N*-dimethyl-2-[5-(1,2,4- triazol-1-ylmethyl)-1*H*-indol-3-yl]ethylamine.

(10) The relevant dates and information pursuant to 35 U.S.C. 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) Investigational New Drug Application 40,458 for rizotriptan benzoate was submitted on August 31, 1992, and the receipt thereof was acknowledged on September 1, 1992. The IND became effective on October 1, 1992. New Drug Application (NDA 20-864) for MAXALT® (Rizatriptan Benzoate) and New Drug Application (NDA 20-865) for MAXALT-MLT™ (RAPIDISC) (Rizatriptan Benzoate) were submitted on June 30, 1997. New Drug Application (NDA 20-864) for MAXALT® (Rizatriptan Benzoate) and New Drug Application (NDA 20-865) for MAXALT-MLT™ (RAPIDISC) (Rizatriptan Benzoate) were approved on June 29, 1998.

(11) As a brief description of the activities undertaken by Applicant, Merck & Co., Inc., during the applicable regulatory review period, attached hereto as "Attachment D" is a chronology of the major communications between the Applicant and the FDA from August 31, 1992 to June 29, 1998.

(12)(A) Applicant is of the opinion that U.S. Patent 5,298,520, is eligible for extension under 35 U.S.C. 156 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. 156(a)

U.S. Patent 5,298,520 claims the approved products and a method of using such products.

(b) 35 U.S.C. 156(a)(1)

The term of the U.S. Patent 5,298,520 has not expired before the submission of this application.

(c) 35 U.S.C. 156(a)(2)

The term of the U.S. Patent 5,298,520 has never been extended under this provision of the law.

(d) 35 U.S.C. 156(a)(3)

The application for extension is submitted by the Applicant Merck & Co., Inc., which is acting on behalf of the assignee of record, in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. 156(a)(4)

The products, MAXALT® (Rizatriptan Benzoate) and MAXALT-MLT™ (RAPIDISC) (Rizatriptan Benzoate), have been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. 156(a)(5)(A)

The commercial marketing or use of the products, MAXALT® (Rizatriptan Benzoate) and MAXALT-MLT™ (RAPIDISC) (Rizatriptan Benzoate), after the regulatory review period, is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) under which such regulatory review period occurred.

(g) 35 U.S.C. 156(c)(4)

No other patent has been extended for the same regulatory review period for the products, MAXALT® (Rizatriptan Benzoate) and MAXALT-MLT™ (RAPIDISC) (Rizatriptan Benzoate).

(B) The length of extension of the patent term of U.S. Patent 5,298,520 claimed by Applicant is 153 days. The length of the extension was determined pursuant to 37 C.F.R. 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. 156(g)(1)(B) began on October 1, 1992 and ended on June 29, 1998 which is a total of 2098 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. 156(g)(1)(B)(i) began on October 1, 1992 and ended June 30, 1997, which is 1733 days; and

(ii) The period of review under 35 U.S.C. 156(g)(1)(B)(ii) began on June 30, 1997 and ended on June 29, 1998, which is 365 days;

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph 12(B)(a) above (2098 days) less:

(i) The number of days in the regulatory review period which were on and before the date on which the patent issued (March 29, 1994) which is 545 days, and

(ii) The number of days during which applicant did not act with due diligence which is 0 days, and

(iii) One-half of the period of time resulting from the subtraction of the period of time calculated under (B)(b)(i) (545 days) from the period of time calculated under (B)(a)(i) (1733 days), which is 594 days;

(iv) The regulatory review period is calculated by subtracting the number of days determined in sub-paragraph 12(B)(b)(i)-(iii) from the entire regulatory review period as determined in sub-paragraph 12(B)(a) (which is 2098 days - 545 days - 594 days) which equals 959 days.

(c) The number of days as determined in sub-paragraph 12(B)(b)(iv) (959 days) when added to the term of the patent (January 28, 2012) would result in the date September 13, 2014.

(d) Fourteen (14) years when added to the date of NDA approval (June 29, 1998) would result in the date June 29, 2012;

(e) The earlier date as determined in sub-paragraphs 12(B)(c) and 12(B)(d) is June 29, 2012.

(f) Since the original patent was issued after September 24, 1984, five (5) years when added to the expiration date of the patent (January 28, 2012) would result in the date January 28, 2017;

(g) The earlier date as determined in sub-paragraph 12(B)(e) and 12(B)(f) is June 29, 2012.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

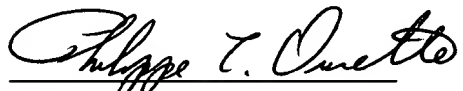
(14) The prescribed fee for receiving and acting upon this application is to be charged to Deposit Account of Applicant as authorized in the attached letter, which is submitted in duplicate.

(15) Correspondence related to this application for extension of the patent term of U.S. Patent 5,298,520 should be addressed to Philippe L. Durette, Reg No. 35,125, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065-0907 (telephone (732) 594-4958).

(16) The instant application for extension of the patent term of U.S. Patent 5,298,520 is being submitted as one original and triplicate copies thereof.

(17) The requisite declaration pursuant to 37 C.F.R. 1.740(b) is attached.

Respectfully submitted,



Philippe L. Durette
Reg. No. 35,125
Attorney for Applicants

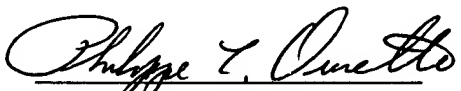
MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-4568 (phone)
(732) 594-2300 (fax)

Date: August 5, 1998

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156 including its attachments and supporting papers is being submitted as one original and triplicate copies thereof.

Date: August 5, 1998



Philippe L. Durette

ATTACHMENT A

(Authorization of Agent and Power of Attorney)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent 5,298,520
Issued:	29 March 1994
To:	Raymond Baker, Victor G. Matassa, Leslie J. Street
Assignee:	Merck Sharp & Dohme Limited
For:	TRIAZOLE CONTAINING INDOLE DERIVATIVES

Assistant Commissioner for Patents

Box: Patent Extension

Washington, D.C. 20231

AUTHORIZATION OF AGENT AND
POWER OF ATTORNEY

Merck Sharp & Dohme Limited a company organized under the laws of England, and having its principal place of business at Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU, United Kingdom, being an owner of record of the above-identified U.S. Letters Patent, hereby authorize and appoint, Merck & Co., Inc., a corporation organized and existing under the laws of New Jersey and having its head office at One Merck Drive, P.O. Box 100, Whitehouse Station, New Jersey 08889-0100, and the Patent Attorneys named below:

Joseph F. DiPrima	(Reg. No. 28,944)
Melvin Winokur	(Reg. No. 32,763)
Philippe L. Durette	(Reg. No. 35,125)

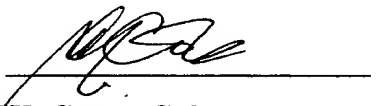
all being employees of Merck & Co., Inc. individually and collectively to be the agents and attorneys of Merck Sharp & Dohme Limited with regard to an

application for extension of term of U.S. Patent 5,298,520 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please address all communications in the above matter to:

Philippe L. Durette
Merck & Co., Inc.
126 East Lincoln Avenue
Rahway, New Jersey 07065-0907

MERCK SHARP & DOHME LIMITED

By: 

Name: W. Gwyn Cole

Title Senior Director, European Patents

Date: 28 July 1998

ATTACHMENT B

(Certificate of Correction
and
US Patent 5,298,520)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,298,520

DATED : March 29, 1994

INVENTOR(S) : Raymond Baker, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On title page, item [22]
Change filing date January 28, 1993 to January 28, 1992.

Attest:

Mayeni V. Turner

Attesting Officer

Signed and Sealed this

Sixth Day of September, 1994

Bruce Lehman

BRUCE LEHMAN

Commissioner of Patents and Trademarks

US005298520A

United States Patent [19]

Baker et al.

[11] Patent Number: 5,298,520

[45] Date of Patent: Mar. 29, 1994

[54] TRIAZOLE CONTAINING INDOLE DERIVATIVES

[75] Inventors: **Raymond Baker**, Much Hadham; **Victor G. Matassa**, Furneux Pelham; **Leslie J. Street**, Harlow, all of England

[73] Assignee: **Merck Sharp & Dohme Limited**, Hertfordshire, England

[21] Appl. No.: **827,187**

[22] Filed: **Jan. 28, 1993**

[30] **Foreign Application Priority Data**

Feb. 1, 1991	[GB]	United Kingdom	9102222
Apr. 3, 1991	[GB]	United Kingdom	9106917
Jun. 21, 1991	[GB]	United Kingdom	9113415
Oct. 23, 1991	[GB]	United Kingdom	9122451

[51] **Int. Cl.**[5] **A61K 31/41**; C07D 403/06

[52] **U.S. Cl.** **514/383**; 514/381; 514/397; 514/323; 546/201; 548/254; 548/312.1; 548/255; 548/266.4

[58] **Field of Search** 548/266.4, 254, 255, 548/336; 546/201; 514/381, 383, 397, 323

[56] **References Cited**

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3,644,403	2/1972	Rodriguez	548/491
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4,453,001	6/1984	Brand et al.	548/466
4,618,617	10/1986	Yamamato	514/364
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0328200	8/1989	European Pat. Off. .
91/188897	12/1991	PCT Int'l Appl. .
2083463A	3/1982	European Pat. Off. .

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Katritzky et al "Heterocyclic Chemistry" Oxford, 1964, pp. 232–233.

Journal of Medicinal Chemistry, vol. 30, No. 1, (Jan. 1987) Washington U.S. *R. A. Glenn, 'Central Serotonin Receptors as Targets for Drug Research'.

A. Doenicke, et al The Lancet, 1988, 1, 1309–11.

J. Neurosci. 7, 894, (1987) 1981.

Arch. Pharm., 342, 8 111 (1990) 1973.

J. Org. Chem., vol. 47, pp. 536–544 (1982) by Jose Elguero, et al., entitled *Synthesis and Physicochemical Properties of 1,2,b-Thiadiazine 1,1-Dioxides.*

Chem. Ber. vol. 111, pp. 1915–1971 (1978) by M. Preiss, entitled *1,2,5-Thiadiazolidin-1,1-dioxid und Homologe.*

Indian J. of Chem., vol. 21B, pp. 941–944 (Oct. 1982) by V. P. Arya,: et al., entitled *Nitroimidazoles; Part V-1-(-1-Methyl-5-nitroimidazol-2-yl)-1,2,4-triazolidin-3,5-diones & Analogues.*

Primary Examiner—Jane T. Fan
Assistant Examiner—C. Chang
Attorney, Agent, or Firm—Robert J. North

[57] **ABSTRACT**

A class of substituted imidazole, triazole and tetrazole derivatives are selective agonists of 5-HT_1-like receptors and are therefore useful in the treatment of clinical conditions, in particular migraine and associated disorders, for which a selective agonist of these receptors is indicated.

6 Claims, No Drawings

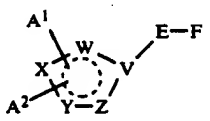
TRIAZOLE CONTAINING INDOLE DERIVATIVES

The present invention relates to a class of substituted imidazole, triazole and tetrazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT_1-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

5-HT_1-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke et al., *The Lancet*, 1988, Vol. 1, 1309–11). The compounds of the present invention, being selective 5-HT_1-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and pediatric migraine.

EP-A-0313397 describes a class of tryptamine derivatives substituted by a five-membered heteroaliphatic ring, which are stated to be specific to a particular type of "5-HT_1-like" receptor and thus to be effective therapeutic agents for the treatment of clinical conditions, particularly migraine, requiring this activity. However, EP-A-0313397 neither discloses nor suggests the imidazole, triazole and tetrazole derivatives provided by the present invention.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



(I)

wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring;

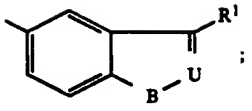
two, three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon provided that, when two of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, then the said nitrogen atoms are in non-adjacent positions within the five-membered ring;

A^1 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $—OR^x$, $—SR^x$, $—NR^xR^y$, $—NR^xCOR^y$, $—NR^xCO_2R^y$, $—NR^xSO_2R^y$, or $—NR^zCTNR^xR^y$;

A^2 represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when two or three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A^2 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $—OR^x$, $—SR^x$, $—NR^xR^y$, $—NR^xCOR^y$, $—NR^xCO_2R^y$, $—NR^xSO_2R^y$, or $—NR^zCTNR^xR^y$;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula

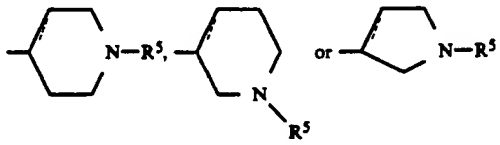


;

U represents nitrogen or $C—R^2$;

B represents oxygen, sulphur or $N—R^3$;

R^1 represents $—CH_2.CHR^4.NR^6R^7$ or a group of formula



in which the broken line represents an optional chemical bond;

R^2, R^3, R^4, R^5, R^6 and R^7 independently represent hydrogen or C_{1-6} alkyl;

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group;

R^z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula $=N.G$; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

The present invention also provides compounds of formula I above wherein three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon;

A^2 represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A^2 represents hydrogen, hydorcarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $—OR^x$, $—SR^x$, $—NR^xR^y$, $—NR^xCOR^y$, $—NR^xCO_2R^y$, $—NR^xSO_2R^y$, or $—NR^zCTNR^xR^y$; and

A^1, E, F, R^x, R^y R^z and T are as defined above.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon

ATTACHMENT C

(Maintenance Fee Payment Receipt)

UNITED STATES DEPARTMENT OF COMMERCE
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PAYOR NUMBER
000210

P75N

MERCK & CO., INC.
PATENT DEPARTMENT
P.O. BOX 2000
RAHWAY NJ 07065-0907

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,298,520	183	1020	----	07/827,187	03/29/94	01/28/92	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	T-1092Y

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231**

ATTACHMENT D

(Chronology of Major Events)

MAXALT (rizatriptan benzoate)
Chronology of Major Events

IND 40,458	NDAs 20-864/20-865	DATE	EVENT
X		8/31/92	Original IND for MK-0462 was submitted.
X		9/8/92	FDA letter was sent to MRL acknowledging receipt on 9/1/92 of the original IND.
X		10/21/92	In response to FDA comments on original IND, pharmacokinetic data following higher doses not provided in the IND was submitted.
X		4/13/93	Nonclinical reproductive toxicology information was submitted.
X		6/8/93	FDA Reviewer comments on the original IND were received.
X		8/6/93	MRL responses to FDA comments dated 6/8/93 were submitted.
X		8/24/93	Original Export Petition for MK-0462 was submitted.
X		10/13-14/93	Telephone conversations with FDA concerning serious adverse experience reports from an ongoing study with MK-0462 in the United Kingdom
X		10/15/93	Ancillary pharmacology study information was submitted.
X		5/11/94	Dose selection information for rat/mouse carcinogenicity studies was submitted.
X		8/23/94	FDA comments to 5/11/94 submission were received.
X		10/5/94	MRL responses to FDA comments regarding dose selection for rat/mouse carcinogenicity studies were submitted.
X		12/9/94	Background package and Request for End of Phase II meeting were submitted.
X		1/20/95	Telephone request from FDA for additional information on rat/mouse carcinogenicity studies
X		2/9/95	Additional background information regarding MRL dose selection for rat/mouse carcinogenicity studies was submitted as requested by FDA in a 1/20/95 telephone conversation.
X		2/15/95	End of Phase II conference was held at FDA in Rockville, MD
X		4/26/95	Background Package and confirmation of End of Phase II meeting to discuss biopharmaceutics program.
X		5/10/95	MRL minutes of 2/15/95 End of Phase II conference were submitted.
X		5/11/95	End-of-Phase II meeting held with FDA Biopharmaceutics group
X		5/18/95	Information requested by FDA to enable final review of MRL dose selections for rat and mouse carc studies was submitted.

X	6/5/95	MRL minutes of 5/11/95 Biopharmaceutics meeting were submitted.
X	12/7/95	Request for End of Phase II meeting to discuss development program with MK-0462 RAPIDISC formulation was submitted.
X	2/5/96	FDA letter confirming requirement that mouse carcinogenicity study protocols were to be 24 months in duration was received.
X	2/7/96	FDA letter was received stating concurrence with MRL's proposal for clinical development of the RAPIDISC formulation of MK-0462 was received, indicating an End of Phase II meeting would be unnecessary.
X	1/26/96	Adverse Experience Report of granulycytosis was submitted to FDA.
X	3/8/96	Additional hematologic information was submitted at the request of FDA relating to the report of an occurrence of granulocytosis submitted on 1/26/96.
X	4/19/96	FDA letter was received containing questions/comments regarding pre-NDA development of the drug synthesis process.
X	5/10/96	Data Analysis Plan for the Phase III Development program for MK-0462 was submitted.
X	6/14/96	MRL responses to FDA comments/questions received on 4/19 were submitted.
X	7/29/96	MRL submitted to FDA a letter confirming termination of the oral mouse carcinogenicity study at week 100 due to no-treatment related mortality.
X	8/12/96	FDA letter was received requesting characterization and quantification of the degradate L-783,540 under conditions of clinical use for the RAPIDISC formulation.
X	9/9/96	MRL submitted request for a pre-NDA meeting
X	9/26/96	MRL submitted a background package to FDA to facilitate preparation for pre-NDA meeting
X	10/24/96	Pre-NDA Meeting held with FDA in Rockville, MD
X	11/11/96	MRL submitted background information to FDA to characterize the degradate L-783,540
X	11/12/96	FDA response was received with comments/questions about CMC amendments for MK-0462 5mg and 10mg tablets.
X	12/20/96	MRL submitted a request for a pre-NDA meeting with FDA to discuss CMC issues, along with a background package.
X	12/20/96	MRL minutes of the 10/24/96 pre-NDA meeting were submitted.
X	1/10/97	FDA Biopharm comments from 10/24/96 pre-NDA meeting were received.
X	1/29/97	FDA letter was received indicating the RAPIDISC NDA would be unfileable without final

			toxicology reports from planned developmental toxicity studies in rat and rabbit to characterize the degradate L-783-540.
X		2/7/97	MRL submitted a request for meeting to discuss, and offered a demonstration of, the planned MRL electronic submission for MAXALT, along with a background package.
X		2/18/97	MRL submitted a letter confirming the intention to accelerate the timeline for completion of rat and rabbit toxicology studies requested by FDA in order to allow their inclusion in the upcoming NDA.
X		2/28/97	MRL submitted a waiver request allowing for the electronic (only) submission of Items 11 and 12 in the upcoming NDA.
X		3/18/97	MRL submitted a request for waiver of 21 CFR 206.10 requiring imprinting of solid dosage form for the MAXALT RAPIDISC formulation.
X		3/27/97	Waiver request for electronic submission of Items 11 and 12 was approved
X		4/28/97	MRL submitted a SAS Transport Files Pilot CD representative of what would later appear in the NDAs.
X		5/30/97	FDA denied request for waiver of requirement for embossing of the RAPIDISC dosage form for reasons of clinical safety.
	X	6/20/97	MRL submitted User Fees for NDAs 20-864 and 20-865
	X	6/30/97	MRL submitted two original New Drug Applications (NDAs) for MAXALT 5mg and 10mg tablets (NDA 20-864) and 5mg and 10mg RAPIDISC (NDA 20-865).
	X	7/15/97	Electronic versions of NDAs 20-864 and 20-865 were submitted
	X	8/8/97	FDA letter acknowledging receipt of the two NDAs was received.
X		8/18/97	FDA letter was received accepting MRL's proposal dated 3/18/97 for embossing of RAPIDISC dosage form
	X	8/20/97	MRL submitted information to Division of Scientific Investigations (DSI) as requested by Dr. Robert Young, FDA
	X	9/11/97	MRL requested a categorical exclusion from the requirement to provide an environmental assessment for MAXALT.
X		10/1/97	MRL submitted a request for Agency review and comment on a proposed development program for the treatment of migraine attacks in adolescents.
	X	10/17/97	MRL submitted additional site-specific information to DSI
X		10/29/97	FDA letter was received with comments on MRL's development program for MAXALT in the treatment of adolescent migraine

X	10/31/97	MRL submitted a Safety Update Report (SUR) for MAXALT
X	11/13/97	MRL submitted an electronic version of the SUR.
X	11/25/97	FDA letter was received with initial comments/questions regarding the CMC sections of the NDAs.
X	11/26/97	MRL submitted results of the PPI comprehension tests conducted for the MAXALT PPIs.
X	12/26/97	MRL submitted responses to CMC comments/questions listed in FDA letter received 11/25
X	12/29/97	MRL submitted updated stability data for MAXALT Tablets as committed to at the pre-NDA CMC meeting on 2/25/97
X	2/2/98	MRL submitted efficacy datasets for Protocols 022,025 and 029 providing for the additional variable of "time to rescue"
X	2/11/98	MRL submitted an Amendment to a Pending Application updating the Package Circular to include Kaplan-Meier plots in the Clinical Studies section
X	3/18/98	MRL submitted a request for permission to import launch quantities of both MAXALT dosage forms prior to NDA approval.
X	3/20/98	MRL submitted methods validation samples of drug product to Philadelphia and St Louis FDA test labs for analysis
X	3/25/98	MRL submitted additional site-specific information (for international sites) to Dr. Robert Young, DSI, FDA
X	3/27/98	MRL submitted corrected efficacy datasets for protocols 022, 025 and 029
X	4/2/98	MRL submitted an amendment to a pending application providing for revised labeling per request from Dr. Doris Bates, FDA
X	4/6/98	MRL submitted an amendment to a pending application providing revised labeling containing corrected Kaplan-Meier plots
X	4/6/98	MRL submitted updated dissolution data on clinical and stability batches in response to an Agency request (Dr. Tammara)
X	4/24/98	In response to an FDA request, MRL submitted an amendment to a pending application providing for labeling revisions to align MAXALT labeling with the format and content established by FDA for the 5-HT_1 receptor agonist class of products.
X	4/27/98	MRL submitted information on several biopharmaceutics studies for MAXALT, in response to an Agency request (Dr. Tammara)
X	5/14/98	Based on discussions with FDA, MRL submitted an amendment to a pending application providing revised labeling that included additional

		efficacy data, adverse experience information and oral contraceptive interaction data with regard to efficacy.
X	5/15/98	FDA letter was received granting approval for importation of MAXALT drug product for pre-launch packaging.
X	5/29/98	In response to FDA comments, MRL submitted an amendment to a pending application containing a revised Clinical Studies section, updated hepatic impairment information, and a revised absorption ratio.
X	6/1/98	MRL submitted a revised PPI aligned with the current package circular.
X	6/4/98	MRL submitted an amendment to a pending application providing packaging component labeling for MAXALT 5mg and 10mg tablets samples.
X	6/8/98	In response to an FDA request, MRL submitted an amendment to a pending application in which a single Patient Information leaflet was created applicable to both dosage forms.
X	6/15/98	In response to FDA comments, MRL submitted an amendment to a pending application containing a revised Physician's Information circular, reflecting FDA comments and proposed wording for theBinding of Melanin-Containing Tissues, Impairment of Fertility, and Pregnancy Category subsections.
X	6/24/98	MRL submitted an amendment to a pending application providing a revised package circular and Patient Information leaflet based on recommendations from Dr. R. Levin, FDA.
X	6/29/98	FDA Approval letter for NDAs 20-864 and 20-865 were received.

PLEASE NOTE:

* Throughout the review process, unofficial emails were exchanged between MRL and FDA on a daily and sometimes hourly basis. All FDA requests for data, information, and clarification were delivered in a timely fashion, and many were submitted as "official" submissions as noted in the chronology above. The chronology does not capture each individual email.